Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine and placebo: evidence from randomized clinical trials

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Authors' objectives

To estimate the healing and relapse rates in the acute and maintenance treatment of gastroesophageal reflux disease (GERD) with the newer proton-pump inhibitors (PPIs) lansoprazole, rabeprazole and pantoprazole, compared with omeprazole, ranitidine and placebo.

Searching

MEDLINE was searched from June 1979 to June 2000 with no language restrictions, using the following keywords and MeSH: 'PPI', proton pump inhibitors', 'rabeprazole', 'omeprazole', 'pantoprazole' and lansoprazole'; 'relapse rates', 'healing rates', 'peptic ulcer', 'peptic acid', 'peptic related disorders', 'esophagitis', 'GERD', 'reflux esophagitis' and 'gastrointestinal symptoms'; and 'clinical trials', 'randomized clinical trials', 'multicenter studies', 'meta-analysis', 'pharmacoeconomic studies' and 'reviews'. In addition, the reference lists of all relevant papers were searched for additional studies.

Study selection

Study designs of evaluations included in the review

Randomised controlled clinical trials (RCTs) were included in the review. Studies of pharmacokinetics (dose-ranging studies), pharmacodynamics or pH were not considered. Abstracts with insufficient data, preliminary reports, or studies reported more completely elsewhere were also excluded.

Specific interventions included in the review

For studies of acute therapy, at least one treatment arm had to include a newer PPI versus omeprazole or ranitidine. For studies of maintenance therapy, at least one treatment arm had to include a PPI versus omeprazole, ranitidine, or placebo. Studies on PPIs combined with antibiotics for the eradication of Helicobacter pylori infection were excluded.

For acute therapy, the actual interventions included in the review were: rabeprazole (20 mg/day) versus omeprazole (20 mg/day) (2 studies); pantoprazole (40 mg/day) versus omeprazole (20 mg/day) (2 studies); lansoprazole (30 mg/day) versus omeprazole (20 to 40 mg/day) (4 studies); rabeprazole (20 mg/day) versus ranitidine (600 mg/day) (1 study); pantoprazole (40 mg/day) versus ranitidine (300 mg/day) (1 study); omeprazole (10 to 60 mg/day) versus ranitidine (300 mg/day) (10 studies); lansoprazole (30 to 60 mg/day) versus ranitidine (300 to 600 mg/day) (6 studies).

For maintenance therapy, the actual included interventions were: rabeprazole (10 or 20 mg/day) versus omeprazole (20 mg/day) (1 study); lansoprazole (15 or 30 mg/day) versus omeprazole (20 mg/day) (2 studies); rabeprazole (10 or 20 mg/day) versus placebo (1 study); omeprazole (10 or 20 mg/day) versus placebo (4 studies); lansoprazole (15 or 30 mg/day) versus placebo (2 studies), omeprazole (20 mg/day) versus ranitidine (300 to 450 mg/day) (4 studies); lansoprazole (15 or 30 mg/day) versus ranitidine (600 mg/day) (1 study).

Participants included in the review

Studies of patients with an endoscopically confirmed diagnosis of GERD were included in the review. In practice, all of the studies focused on an adult population; the age ranged from 40 to 62 years (mean 52; standard deviation 5.3) for studies of acute therapy and from 44 to 61 years (where reported) for maintenance therapy. Thirty-nine per cent of the studies included women, and 81% required the presence of active disease. In relation to the maintenance phase, all studies required endoscopic healing for enrolment in the phase, but the definition of healing varied: some studies considered erythematous mucosa to be healed when all erosions had disappeared, while others required complete normalisation of the mucosa (Savary-Miller grade 0).

In relation to the exclusion criteria used in the individual trials, 75% reported excluding participants with concurrent systemic diseases, 72% those with concurrent acid-related diseases, 63% those with recent surgery, 60% those who had received previous treatment with histamine2-receptor antagonists or PPIs, 54% pregnant women, 50% breast-feeding women, 41% those with pyloric stenosis, and 38% users of non-steroidal anti-inflammatory drugs.

Outcomes assessed in the review

The included papers had to assess ulcer healing by endoscopy. Papers that reported symptoms only and did not confirm healing endoscopically were included in the analysis of symptoms improvement and resolution, but were excluded from the healing rate analysis.

For acute therapy, the primary outcomes assessed were heart burn resolution and ulcer healing. The methods used to collect and analyse the clinical symptoms varied between studies: 58% used interviews, 52% patient diary cards, and 6% visual analogue scales. Some studies reported using more than one of these methods. Likewise, the definition of ulcer healing varied between studies with 17% requiring complete epithelialisation of the ulcer (Savary-Miller grade 0 or 1), whereas others (83%) used a definition based upon Savary-Miller grade 2 or higher.

For the maintenance phase, the outcome assessed was the number of patients with an endoscopically confirmed diagnosis of relapse. This was analysed in two time periods: from randomisation to 6 months and from 6 to 12 months. Again, the definition of healing varied.

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed the primary studies for inclusion; the decision was made with knowledge of the trial results. The authors did not state how any disagreements were resolved.

Assessment of study quality

The authors stated that they assessed the adequacy of the randomisation process by comparing the distribution of age, gender, alcohol use and cigarette smoking reported in each of the primary studies. However, no further validity assessment was reported. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction

Two reviewers independently extracted the data and resolved any discrepancies by consensus. The information retrieved covered study design, population characteristics, diagnosis, disease severity, acute or maintenance treatment, PPI and comparator regimens, clinical outcomes, methods used to measure outcomes, and confounding variables such as alcohol use, cigarette smoking and caffeine use.

In studies of acute therapy, the results were extracted for both intention-to-treat and per-protocol analyses for each outcome where these data were reported.

Methods of synthesis

How were the studies combined?

For each study of acute therapy, ulcer healing and heartburn relief rates were calculated, whereas for the studies of maintenance therapy, ulcer relapse rates were generated. The rate ratios (RRs) and 95% confidence intervals (CIs) for acute and maintenance therapy with lansoprazole, rabeprazole and pantoprazole versus omeprazole and ranitidine were estimated at specific time points. The pooled rate analysis focused on the recommended dose of each PPI: lansoprazole 30 mg/day, rabeprazole 20 mg/day, pantoprazole 40 mg/day, and omeprazole 20 mg/day. Chi-squares and 95% CIs were calculated using the method of Miettinen (see Other Publications of Related Interest no.1). A P-value of less than 0.05 was considered significant for all statistical tests, and no adjustments were made for multiple comparisons.

Since there was no statistically-significant evidence of heterogeneity, the healing rates were pooled across studies by time point (4 and 8 weeks), with individual trial results being weighted by the inverse of the variance of the RR for each trial. The overall RR was then estimated by dividing the weighted average healing rates or heartburn relief rates for the treatments being compared with the estimates for omeprazole and ranitidine. These RRs were assessed using the Mantel-

Haenszel chi-squared test, and 95% CIs were calculated using the exact method (see Other Publications of Related Interest no.1).

The possibility of publication bias was assessed by plotting the RRs against the sample size. To assess the robustness of the findings over time, the studies were ordered chronologically and a cumulative meta-analysis undertaken, with a plot of cumulative estimates over time being constructed. To identify any studies that exerted a disproportionate influence on the summary treatment effect, the authors deleted individual studies one at a time. In order to investigate the consequences of including abstracts of studies for which full reports were not available, the authors also excluded data from these trials in the secondary analyses.

How were differences between studies investigated?
Differences between the studies were examined using the Wald chi- squared test for statistical homogeneity (see Other Publications of Related Interest no.2). No significant degree of heterogeneity was found.

Results of the review

In total, 41 RCTs (n=11,237) were included in the review; 26 (n=6,797) examined interventions for acute therapy and 15 (n=4,440) assessed interventions for maintenance therapy.

Acute therapy.

Heartburn resolution: the overall heartburn relief RR at 4 weeks for the newer PPIs, compared with omeprazole, was 1.02 (95% CI; 0.94, 1.11). The rate of heartburn resolution was 1.53 (95% CI: 1.37, 1.72) times higher with the PPIs (newer PPIs and omeprazole) than with ranitidine.

Ulcer healing: these analyses were reported using the intention- to-treat approach. Healing RRs for the newer PPIs were obtained at 4 and 8 weeks. At 4 weeks, compared with omeprazole, the overall RR was 1.04 (95% CI: 0.99, 1.10) for lansoprazole, 0.92 (95% CI: 0.85, 1.00) for rabeprazole, and 0.96 (95% CI: 0.85, 1.08) for pantoprazole. Compared with ranitidine, the healing RRs were 1.84 (95% CI: 1.63, 2.08), 1.61 (95% CI: 1.27, 2.05), 1.31 (95% CI: 1.03, 1.73) and 1.87 (95% CI: 1.64, 2.15) for lansoprazole, rabeprazole, pantoprazole and omeprazole, respectively. The overall healing RRs for the PPIs included in more than one paper were statistically significant compared with ranitidine; the rates were 1.83 (1.63 to 2.08) for lansoprazole 30 mg/day, and 1.81 (1.54 to 2.13) and 1.92 (1.49 to 2.51) for omeprazole 20 and 40 mg/day, respectively. At 8 weeks, compared with omeprazole 20 mg/day, the overall healing RR was 1.02 (95% CI: 0.98, 1.06) for lansoprazole 30 mg/day, 0.93 (95% CI: 0.87, 1.00) for rabeprazole 20 mg/day, and 0.98 (95% CI: 0.90, 1.07) for pantoprazole 40 mg/day. Compared with ranitidine, the RRs were 1.62 (95% CI: 1.46, 1.76), 1.36 (95% CI: 1.20, 1.54) and 1.60 (95% CI: 1.33, 1.96) for lansoprazole, rabeprazole and pantoprazole, respectively; for omeprazole the RR was 1.58 (95% CI: 1.41, 1.78).

Maintenance therapy.

The relapse rates with lansoprazole were lower than those with ranitidine or placebo and no different from those with omeprazole at 6 months. Compared with ranitidine and placebo, the relapse rates were statistically significantly lower for all newer PPIs in the individual studies ($P<0.05$). Eighty-seven per cent of patients treated with the newer PPIs were in endoscopically confirmed remission at 12 months. In contrast, 40% of patients receiving ranitidine and 28% receiving placebo were in remission at 12 months.

In terms of publication bias, there was no tendency for increasing RRs with lansoprazole, rabeprazole or pantoprazole in comparison with omeprazole, irrespective of the sample size. Similarly, studies comparing a PPI with ranitidine showed healing RRs that favoured the PPIs, irrespective of the number of patients in the trial. The results of the cumulative RR analysis indicated that the estimate was not distorted in one direction or the other. The sensitivity analysis, where data reported in abstract form were removed, indicated that there was no difference in the estimates of effect when these studies were excluded.

Cost information

NO.

Authors' conclusions
The newer PPIs were of similar efficacy to omeprazole in terms of heartburn control, healing rates and relapse rates. All of the PPIs were superior to ranitidine and placebo in healing erosive oesophagitis and decreasing relapse rates.

CRD commentary
The authors addressed a clear review question, which was well-defined in terms of the interventions, participants, study designs and outcome measures to be assessed. The literature search was adequate and no language restrictions were applied, but the restriction to one database means that other relevant studies could have been missed. Two reviewers assessed the relevance of primary studies for inclusion in the review, thus minimising any bias in the selection process. However, although the authors described a form of validity assessment, it was unclear as to how this was undertaken. In addition, the quality of the studies was not apparently used to weight the results in the meta-analysis.

Adequate details on the characteristics of the primary studies were tabulated, allowing the reader to assess whether the authors' results and conclusion are consistent with the evidence base reviewed. The statistical methods used were appropriate, although no adjustments were made for multiple comparisons. This would increase the size of the RRs where multiple comparisons were being made between interventions. The authors also assessed heterogeneity and adequately examined publication bias. Overall, despite the few biases that could have been introduced into the review process, this was a well-conducted review. The authors' results and conclusions appear consistent with the evidence base reviewed.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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Other publications of related interest
1. Miettinen OS. Theoretical epidemiology. In: Principals of occurrence research in medicine. New York: Delmar Publishers; 1985. p. 155-83. 2. Greenland R, Rothman KJ. Testing homogeneity. In: Rothman KJ, Greenland S, editors. Modern epidemiology. 2nd ed. Philadelphia: Williams and Wilkins; 1998. p. 275-7.

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